DRUG REPURPOSING – NEW WINE IN OLD BOTTLES

Bryan Hanley, ACTA
a.b.hanley@acta.nl

Michael Graz*, Biophys Ltd
michael@biophys.co.uk

"And no one pours new wine into old wineskins. Otherwise, the wine will burst the skins, and both the wine and the wineskins will be ruined. No, they pour new wine into new wineskins."

Mark 2:22

INTRODUCTION

The concept that drugs can be 'repurposed' to create added clinical and commercial value through the establishment of new medical uses for already known drugs is one which is superficially attractive. Drugs which have already been approved will have passed all the appropriate regulatory hurdles and this should mean that they can be brought to market more quickly and time and resources can be saved in the use of available drugs rather than having to synthesise or produce sufficient quantities of new bioactive entities de novo. Nonetheless, it is important to bear certain caveats in mind including the nature of drug screening, the delivery of drugs in a pharmacological dose to the site in the body where they are required (this is underpinned by ADME – Absorption, Distribution, Metabolism and Excretion – studies), and the therapeutic window which, for some purposes may be too narrow to allow a drug to be successfully repurposed.

DRIVERS FOR DRUG REPURPOSING

A major factor in the use of repurposing for drugs is the cost of drug development. It has been estimated (based on published data) that the R&D costs of developing a drug ranged from $161 million to $4.54 billion. The highest costs were associated with Drug Discovery and Optimization (50%) while pre-clinical and clinical trials accounted for the bulk of the remainder (49%). The cost of obtaining FDA approval was only 1.3% of the total cost [1]. If a bioactive can be repurposed in its original form for a new therapeutic endpoint then considerable costs can be saved [2]. It should be noted, however, that the clinical costs also include those drugs that are abandoned because of safety and lack of efficacy in a range of tests. It has been estimated that the failure rate for new drugs is around 90%. Repurposing (aided by AI and other Structure: Activity techniques) can greatly improve the hit rate, shorten the time to market and provide new clinical insights.

A recent study of drug repurposing suggested that there were a number of factors that influenced the drive for repurposing [3]. These included "the ability to form multi-partner collaborations (n=38), access to compound databases and database screening tools (n=32), regulatory modifications (n=5)." One significant facilitator for the re-examining of chemical entities for new purposes was the need for the rapid development of effective therapies to counter the Covid epidemic, however even before the pandemic, a report by the Association of Medical Research Charities (AMRC) in the UK [4], suggested that a licensing route should be established for repurposed, off-patent drugs and that "A UK Catalyst Fund should be explored to establish the UK as a leader in medicines repurposing".

Even before the pandemic, it was estimated that repurposed drugs generated around 25% of the annual revenue for the pharmaceutical industry [5]. In addition to the reduced cost, perhaps the most significant driver for repurposed drugs is the significantly shortened drug development timeline. In particular, if the pharmacological use is already known (but not commercially exploited) and the pharmaceutical dose is lower or equivalent to the existing approved usage level, some of

the preclinical testing and safety evaluation becomes unnecessary.

THE PANDEMIC AND DRUG REPURPOSING

Following the growth of the pandemic, a number of initiatives were started to try to find existing drugs that could be repurposed. Such variation of use is more likely to be successful if the original use of the drug encompasses some clinical aspect of the virus aetiology.

In the US the CORONA (COvid19 Registry of Off-label & New Agents) project was launched in March 2020 to track clinical studies designed to lessen the impact of Covid[6]. The stated aim of the project was to provide a data repository for trials related to Covid-19 and to thereby facilitate the more rapid development of effective therapeutics. The RECOVERY (Randomised Evaluation of Covid-19 Therapy) and the SOLIDARITY trial were set up to test multiple drug treatments for Covid. These trials have indicated that hydroxychloroquine, lopinavir–ritonavir, and interferon did not reduce mortality. The trials have also shown how prevalent ideas about some types of therapeutics can take hold. One example is that of hydroxychloroquine. Data suggests that one in three patients globally has received hydroxychloroquine, despite only one of 18 randomised trials showing an effect or benefit.

One of the issues with Covid (and long Covid, indeed) is the long list of co-morbidities associated with the infection. In addition to respiratory symptoms, there is an apparent association between infection and cardiovascular disease, kidney damage, hypertension and diabetes. There have been a range of studies that have implicated Covid infection with several subsequent cardiovascular events including myocarditis, heart failure, arrhythmia, acute coronary syndrome, and venous thromboembolism. It has, therefore, been suggested that repurposing of drugs to deal with the pathologies resulting from Covid infection rather than just the infection itself is a valid approach[7].

REPURPOSING WITHIN AND OUTSIDE CLINICAL AREAS.

Where a mechanism (or even a side effect) of a specific drug has been documented, its application to related conditions can be predicted with a higher degree of certainty. For example, in the case of the drug **pembrolizumab**, it was originally developed as a treatment for advanced melanoma. It is now used for a range of cancers including lung and cervical cancer and lymphoma. Its mechanism of action (activating a T-cell mediated immune response against tumour cells) has allowed it to be tested against a number of cancer types for which such an approach can be predicted to be successful. There are other examples within the cancer field.

The antibiotic, **clarithromycin** has also been shown to have activity against some types of cancer (often in a combination therapy with other drugs). **Methotrexate** is an antirheumatic drug that is widely used for the management of autoimmune and chronic inflammatory disorders. It has been used in the treatment of cardiovascular disease by reducing systemic inflammation (but should not be used to prevent cardiovascular events in the general population)[8] and, perhaps most recently, as a means of damping down the inflammatory response resulting from Covid infection[9].

Statins are used to lower cholesterol but have also been found to be efficacious in a range of other clinical effects including reduction of inflammation, immunomodulation and even as antimicrobials[10]. At the root of much of their activity lies their biochemical mechanism as competitive HMG-CoA reductase (HMGCR) inhibitors.

CONCLUSION

Repurposing drugs may be a useful and interesting way of developing new therapeutic approaches without having to have all the skills (and costs) of a full-blown drug discovery programme. Rapid (essentially random) screening can certainly help to identify potential lead compounds but a better approach is to make use of the knowledge base built up around a given drug in terms of its biochemical mechanism of action, side effects and other potential targets. In this way both clinical and economic advantages may accrue. Care must be taken to understand as much as possible about the disease and the 'not new' therapeutic, if one is to avoid the consequences of pouring "new wine into old wineskins".

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